Osteoporosis is a common disease with a strong genetic component. Twin studies have shown that genetic factors play an important role in regulating bone mineral density (BMD), ultrasound properties of bone, skeletal geometry, and bone turnover as well as contributing to the pathogenesis of osteoporotic fracture itself. These phenotypes are determined by the combined effects of several genes and environmental influences, but occasionally, osteoporosis or unusually high bone mass can occur as the result of mutations in a single gene. Examples are the osteoporosis-pseudoglioma syndrome, caused by inactivating mutations in the lipoprotein receptor-related protein 5 gene and the high bone mass syndrome, caused by activating mutations of the same gene. Genome-wide linkage studies in man have identified loci on chromosomes 1p36, 1q21, 2p21, 5q33-35, 6p11-12, and 11q12-13 that show definite or probable linkage to BMD, but so far, the causative genes remain to be identified. Linkage studies in mice have similarly identified several loci that regulate BMD, and a future challenge will be to investigate the syntenic loci in humans. A great deal of research has been done on candidate genes; among the best studied are the vitamin D receptor and the collagen type I α1 gene. Polymorphisms of vitamin D receptor have been associated with bone mass in several studies, and there is evidence to suggest that this association may be modified by dietary calcium and vitamin D intake. A functional polymorphism affecting an Sp1 binding site has been identified in the collagen type I α1 gene that predicts osteoporotic fractures independently of bone mass by influencing collagen gene regulation and bone quality.

An important problem with most candidate gene studies is small sample size, and this has led to conflicting results in different populations. Some researchers are exploring the use of meta-analysis to try and address this issue and gain an accurate estimate of effect size for different polymorphisms in relation to relevant clinical endpoints, such as BMD and fracture. From a clinical standpoint, advances in knowledge about the genetic basis of osteoporosis are important, because they offer the prospect of developing genetic markers for the assessment of fracture risk and the opportunity to identify molecules that will be used as targets for the design of new drugs for the prevention and treatment of bone disease. (J Clin Endocrinol Metab 87: 2460–2466, 2002)

Evidence from twin and family studies indicates that genetic factors play an important role in the regulation of bone mineral density (BMD) and other skeletal phenotypes relevant to the pathogenesis of fragility fractures. For example, the heritability of BMD at the spine and hip has been estimated to lie between 70 and 85%, with values of 50–60% for wrist BMD (1–3). Factors such as body mass index, age at menarche (4), and age at menopause (5) have all been shown to be significantly affected by genetic factors in twin studies, and estimates of heritability for other fracture-related phenotypes such as quantitative ultrasound properties of bone, hip axis length, and other aspects of femoral neck geometry have ranged from 60–85% (1, 6). The heritability of serum PTH and 1,25-dihydroxyvitamin levels is also high, ranging from 60–65%, as is the heritability of biochemical markers of bone turnover where values have ranged from 29% for serum osteocalcin to 74% for bone-specific alkaline phosphatase (7). Longitudinal studies of axial bone loss in perimenopausal women have shown that most of the variance is unexplained by environmental variables (8). Although this suggests that genetic factors may also play a role in regulating bone loss, direct evidence in favor of this is conflicting. A small twin study by Kelly et al. (9) showed evidence for a significant genetic effect on changes in axial bone density with age, whereas studies by Christian et al. (10) showed no evidence for a genetic effect on radial bone loss in aging male twins. Further work is required to determine whether genetic factors do indeed contribute significantly to the regulation of bone loss.

The role of genetic factors in the pathogenesis of fracture has also been studied. Family history of hip fracture has been consistently shown to be a risk factor for fracture, independent of BMD in population-based studies (11–13), and the heritability of fracture itself has been estimated to lie between 25 and 35% on the basis of twin and family studies (13, 14). This figure is much lower than the heritability of the skeletal phenotypes that predispose to fracture, probably because of the importance of fall-related factors in determining fracture risk. Fragility fractures are however, a prominent feature of some rare diseases that are primarily genetic in nature, including osteogenesis imperfecta, caused by mutations in the type I collagen genes (15) and the osteoporosis-pseudoglioma syndrome caused by mutations in the lipoprotein receptor-related receptor 5 (LRP-5) gene (16).

Identifying genes that predispose to osteoporosis

Several approaches are currently being used to identify the genes that contribute to the pathogenesis of osteoporosis (reviewed in Ref. 17).
Linkage studies in humans. Linkage studies are a tried and tested way of identifying genes responsible for monogenic bone diseases. Recently, they have also been applied to the identification of chromosomal regions which harbor genes that regulate quantitative traits such as bone mass and skeletal geometry. These regions are called quantitative trait loci (QTL). Linkage studies involve genotyping a large number of polymorphic markers, typically spread at 5- to 10-cM intervals throughout the genome and relating inheritance of marker alleles to the inheritance of bone mass within family members. Results of linkage studies are expressed in LOD scores which estimate the ratio of the odds that the candidate locus is linked to the trait under study as opposed to being unlinked. By convention, LOD scores above approximately +3.0 are taken as significant evidence of linkage; those above +1.9 are taken as evidence suggestive of linkage, and those below −2.0 are taken to exclude linkage. An advantage of linkage studies is that they are statistically robust and unlikely to give false positive results. Disadvantages are that they are less suitable for the analysis of complex traits which are genetically heterogeneous and that they have low statistical power to detect genes with modest effects on BMD.

Linkage studies in animals. Genetic linkage studies in experimental animals have long been used in the identification of genes responsible for complex traits, and over recent years, many such studies have been performed in an attempt to identify loci involved in the regulation of BMD in mice (18). The approach used has been to cross laboratory strains of mice with low and high bone density. Mice in the resulting generation (F1) typically have intermediate BMD because they receive a set of high BMD alleles from one parent and a set of low BMD alleles from the other. By interbreeding offspring from the first generation (F1), a second generation (F2) of mice is established with varying levels of BMD, because of segregation of the alleles that regulate BMD in the F2 offspring. A genome-wide search is then performed in the F2 generation, and the inheritance of strain-specific alleles is related to BMD. This approach has several advantages: environment can be carefully controlled, thus minimizing the influence of confounding factors; and large numbers of progeny can be generated, giving excellent statistical power. Also, fine mapping of loci identified can be achieved by backcrossing mice that inherit a locus for regulation of BMD into the background strain and selecting offspring that retain the phenotype for fine mapping studies (18). Although this procedure can be time consuming, it is a very good way of narrowing down the critical interval containing the gene of interest. Possibly, the main disadvantage of genetic mapping studies in mice is the fact that genes which regulate BMD in mice may not necessarily be the same as those which regulate BMD in man.

Candidate gene studies

These involve identifying polymorphisms of a particular gene and relating allelic variants to BMD or osteoporotic fractures in a population-based study or a case control study. Candidate genes are typically chosen on the basis that they have biological effects on bone metabolism or bone cell activity. Candidate gene association studies are relatively easy to perform and can be powered to detect small effects. Disadvantages include the possibility of false positive (or false negative) results due to confounding factors and population stratification. Furthermore, demonstration of an association between a candidate gene and BMD does not necessarily mean that the gene is causally responsible for the effect observed. Associations can also occur as the result of linkage disequilibrium (LD) with a causal gene situated nearby on the same chromosome. LD refers to the phenomenon whereby genes that lie close together tend to be inherited together from one generation to the next. Current evidence suggests that the average extent of LD ranges from 60–350 kb in the human genome, although there is great variation between genomic regions, and significant LD can occasionally extend for up to 1 Mb or more (19). The transmission disequilibrium test (TDT) is a special type of association study that examines the frequency with which individuals inherit alleles suspected to cause disease from a heterozygous parent. In a TDT analysis, the transmitted allele acts as the case, and the nontransmitted allele acts as the control, which makes the TDT immune to the confounding effects of population stratification. These advantages are offset by the fact that the TDT can only be used where parents who are heterozygous for the marker of interest are available. This results in a selected group and limits applicability to the study of late-onset phenotypes such as fracture.

Monogenic bone disease genes

Spectacular progress has been made in identifying genes and chromosomal loci for rare monogenic bone diseases using classical linkage analysis in families (Table 1). Examples include inactivating (recessive) mutations of the LRP-5 gene that have been shown to be responsible for the osteoporosis-pseudoglioma syndrome (16) and an activating mutation of

<table>
<thead>
<tr>
<th>Disease</th>
<th>Locus</th>
<th>Gene</th>
<th>OMIM no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteopetrosis/renal tubular acidosis</td>
<td>8q22</td>
<td>Carbonic anhydrase II</td>
<td>259730</td>
</tr>
<tr>
<td>Pycnodysostosis</td>
<td>1q21</td>
<td>Cathepsin K</td>
<td>601105</td>
</tr>
<tr>
<td>Camurati Engelmann disease</td>
<td>9q13</td>
<td>TGFB1</td>
<td>131300</td>
</tr>
<tr>
<td>Osteopetrosis, autosomal recessive</td>
<td>11q12</td>
<td>TCIRG1</td>
<td>604592</td>
</tr>
<tr>
<td>Sclerosteosis/Van Buchem’s disease</td>
<td>17q12</td>
<td>SOST</td>
<td>605740</td>
</tr>
<tr>
<td>Osteoporosis-pseudoglioma</td>
<td>11q12</td>
<td>LRP-5</td>
<td>259770</td>
</tr>
<tr>
<td>High bone mass</td>
<td>11q12</td>
<td>LRP-5</td>
<td>601884</td>
</tr>
<tr>
<td>Osteopetrosis, autosomal dominant</td>
<td>16p13</td>
<td>CLCN7</td>
<td>602727</td>
</tr>
<tr>
<td>Osteopetrosis, autosomal recessive</td>
<td>16p13</td>
<td>CLCN7</td>
<td>602727</td>
</tr>
</tbody>
</table>

LPR-5 that has been found to be responsible for autosomal dominant inheritance of a syndrome characterized by high bone mass (20). Mutations in the latency-activating peptide domain of the transforming growth factor β1 (TGFβ-1) gene have been shown to be responsible for Camurati-Engelmann disease, a condition characterized by osteosclerosis affecting the diaphysis of long bones (21), whereas mutations affecting the SOST gene and regulatory regions surrounding SOST have been identified as the cause of the sclerosing bone dysplasias, sclerosteosis, and Van Buchem’s disease (22). Inactivating mutations of the TCIRG1 gene, which encodes a subunit of the osteoclast proton pump, have been shown to be responsible for autosomal recessive osteopetrosis (23), whereas inactivating mutations in the CLCN7 gene, encoding a chloride channel expressed in osteoclasts, have been shown to cause severe infantile osteopetrosis. Although haploinsufficiency of CLCN7 does not cause an obvious bone phenotype, specific heterozygous mutations in CLCN7 have been found to cause autosomal dominant osteopetrosis (Albers-Schönberg disease) presumably by exerting a dominant negative effect on chloride channel function (24). Some of these monogenic disease genes may also contribute to regulation of BMD in the normal population. For example, polymorphisms in the TGFβ-1 gene have been found by several groups to be associated with BMD and osteoporotic fracture (25, 26), and the chromosomal region on 11q12–13 that contains the LRP-5 and TCIRG1 genes has been found to be linked to BMD in female sib-pairs (27).

**QTL for BMD and skeletal geometry in humans**

Linkage studies in normal sib-pairs and in extended families with osteoporosis have also been used to identify loci that are linked to BMD (Table 2). Devoto et al. (28) conducted a genome search in a series of affected sib-pairs recruited from several families with a history of osteoporosis and identified loci on chromosomes 1p36, 2p23-p24, and 4q32-34 where the data were suggestive of linkage to spine or hip BMD (LOD scores between +2.5 and +3.5). Further studies by the same group subsequently confirmed evidence of linkage to the 1p36 locus in a second set of sib-pairs (29).

Niu et al. (30) conducted a genome-wide search for loci that regulated forearm BMD in 153 healthy sib-pairs drawn from a Chinese population. In this study, evidence suggestive of linkage to BMD was found on chromosome 2p23–24 (LOD score, +2.15).

**TABLE 2. QTL for BMD in humans identified by genome-wide search**

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>Locus</th>
<th>LOD</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Devoto et al. (28)</td>
<td>Sib-pair</td>
<td>1p36</td>
<td>3.51</td>
<td>Hip BMD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2p23</td>
<td>2.29</td>
<td>Hip BMD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4q33</td>
<td>2.95</td>
<td>Hip BMD</td>
</tr>
<tr>
<td>Niu et al. (30)</td>
<td>Sib-pair</td>
<td>2p21</td>
<td>2.15</td>
<td>Wrist BMD</td>
</tr>
<tr>
<td>Koller et al. (31)</td>
<td>Sib-pair</td>
<td>1q21</td>
<td>3.86</td>
<td>Spine BMD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5q33-35</td>
<td>2.23</td>
<td>Hip BMD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6p11-12</td>
<td>2.13</td>
<td>Spine BMD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11q12-13</td>
<td>2.16</td>
<td>Hip BMD</td>
</tr>
</tbody>
</table>

Koller et al. (31) conducted a genome-wide search for BMD QTL in a sib-pair study of 875 healthy Caucasian and African-American females from 72 families. The highest LOD score attained was +3.86 at chromosome 1q21-23 in relation to lumbar spine BMD. Other LOD scores suggestive of linkage were observed on chromosome 5q33–35 (LOD score, +2.23 with femoral neck BMD) and chromosome 6p11–12 (LOD score, +2.13 with lumbar spine BMD). Koller et al. (27) also conducted a candidate locus linkage study focusing on the high bone mass/osteoporosis pseudoglioma locus on chromosome 11q12–13. In this study, a subgroup of 835 sisters from 374 families who took part in the genome-wide search referred to above (31) showed significant evidence of linkage to 11q12–13 (LOD, +3.50) (27). However, the LOD score fell to +2.16 when the study was expanded to the full population of 875 siblings (31). Possible explanations for this finding include genetic heterogeneity with true linkage in a subset of the population or a false-positive result in the 11q12–13 linkage study.

Further linkage studies in the same population have identified multiple loci for regulation of various aspects of femoral neck geometry (32). These include a locus on chromosome 5q for hip axis length (LOD, 4.3), a locus on chromosome 4q that showed linkage to both hip axis length and mid-femur width (LOD, 3.9 and 3.5, respectively), and a locus on chromosome 17q that was linked to femur head width (LOD, 3.6).

Candidate gene linkage studies have also been performed. Duncan et al. (33) conducted a sib-pair linkage study in 115 probands and 499 of their relatives using polymorphic markers in the vicinity of 23 candidate genes that have been implicated in the regulation of bone mass. The highest LOD score was observed at the PTH receptor 1 locus in chromosome 3p (LOD scores, +2.7–3.5, depending on the method of analysis), but positive LOD scores (above +1.7–1.8) were also observed at the VDR locus, the collagen type I α1 (COLIA1) locus, and the epidermal growth factor locus.

**QTL for BMD in mice**

Linkage studies using inbred strains of mice have identified several loci that regulate bone mass. Klein et al. (34) performed a genome search in 24 inbred strains of mice with varying BMD, generated by crossing the DBA/2 (high BMD) and the C57/BL6 (low BMD) strains. Eight loci showed evidence of suggestive linkage to bone mass, and two loci on chromosomes 7 and 14 showed definite linkage. Similar studies performed on intercrosses between the SAM6/SAMR1 crosses, SAM6/ACKR crosses, and SAM6/SAMP2 crosses identified loci for regulation of bone mass on chromosomes 2, 7, 11, 13, 16, and the X-chromosome (35). Beamer et al. (36) identified four loci that were linked to BMD on a cohort of mice derived from intercross matings of C57BL/6J × CAST/EiJ parents on chromosomes 1, 5, 13, and 15. Currently, QTL for BMD regulation have been identified on almost all mouse chromosomes, and many of these QTL are shared across mouse strains, implying that they contain conserved genes that could be important for regulation of BMD in other species (35). Fine mapping studies of these loci are currently in progress to narrow down the regions of interest and identify...
the genes responsible. When this has been achieved, the next steps will be to determine whether the genes for regulation of BMD in mice are also important regulators of BMD in humans and then to separate the functional from the non-functional polymorphisms within these genes.

Candidate genes for osteoporosis

Candidate gene studies have focused on cytokines and growth factors that regulate bone turnover, genes that encode components of bone matrix, and genes that encode receptors for calcitropic hormones (Table 3). Individual candidate genes that have been implicated in the regulation of bone mass or osteoporotic fractures are discussed in more detail below.

VDR

Vitamin D, by interacting with its receptor, plays an important role in calcium homeostasis by regulating bone cell growth and differentiation, intestinal calcium absorption, and PTH secretion. Morrison et al. (37) identified three common polymorphisms in the 3’ region of the VDR gene, situated between exons 8 and 9, which are recognized by the restriction enzymes BsmI, ApaI, and TaqI. These were found to be associated with circulating levels of the osteoblast-specific protein osteocalcin and bone mass in a twin study and a population-based study. Other studies of VDR in relation to bone mass have been conflicting, however, and a meta-analysis in 1996 concluded that the VDR genotype was associated with relatively modest effects on BMD, amounting to a difference of about 0.15–0.20 Z-score units between genotypes (38). Moreover, a recent family-based study showed no evidence of linkage between the VDR locus and BMD (39). Evidence has been presented to suggest that the association between VDR alleles and BMD may be dependent on calcium and vitamin D intake (40), although the studies in this area have been of limited sample size. A positive association has also been noted between the VDR BsmI-ApaI-TaqI haplotype and the clinically important endpoint of osteoporotic fracture in one study (41), whereas other workers who studied the Apal and/or TaqI polymorphisms found no association with fracture (42). The mechanisms by which the BsmI, TaqI, and Apal polymorphisms affect VDR function are unclear; they may act as markers for RNA stability, because they are in LD with a polymorphic poly A tract in the 3’ untranslated region of the VDR mRNA (37), although data on this issue are conflicting. Another possibility is that they are in LD with functional polymorphisms elsewhere in the VDR gene.

A polymorphism affecting exon 2 of VDR has been described that creates an alternative translational start site, resulting in the production of two isoforms of the VDR protein, which differ in length by three amino acids (43). It is currently uncertain whether these two variants differ significantly in terms of function and association; studies of this polymorphism in relation to BMD and fracture have yielded conflicting results. The exon 2 polymorphism is not in significant LD with the intron 8 and exon 9 polymorphisms.

Another polymorphism has been identified in the promoter of VDR at a binding site for the transcription factor Cdx-2, and this has been associated with BMD in Japanese subjects (44). The Cdx-2 polymorphism appears to be functional because it has been shown to influence DNA protein binding and to modulate gene expression in reporter assays (44). Further studies of this polymorphism in relation to BMD are awaited with interest.

In conclusion, several polymorphisms have been found in the VDR gene, and alleles of this gene have been associated with BMD in several studies. Currently however, the mechanisms by which VDR alleles regulate BMD remain poorly understood.

Type I collagen

The genes encoding type I collagen (COLIA1 and COLIA2) are important candidates for the pathogenesis of osteoporosis. Grant et al. (45) described a common polymorphism affecting a binding site for the transcription factor Sp1 in the first intron of COLIA1 that was more prevalent in osteoporotic patients than in controls. Positive associations between the COLIA1 Sp1 polymorphism, bone mass, and osteoporotic fractures were subsequently reported in several populations, and a meta-analysis showed that the COLIA1 genotype conferred differences in BMD of approximately 0.15 Z-score units per copy of the “s” allele and an increase in fracture risk of approximately 62% per copy of the “s” allele (46). COLIA1 Sp1 alleles have also been associated with other phenotypes relevant to osteoporosis, including postmenopausal bone loss (8, 47), femoral neck geometry (48), and response to etidronate therapy (49).

Significant ethnic differences have been reported in pop-

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**TABLE 3. Candidate genes that have been studied in relation to bone mass**

<table>
<thead>
<tr>
<th>Category</th>
<th>Candidate gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcitropic hormones and receptors</td>
<td>VDR, ER, Aromatase, PTH, PTHR1, Calcitonin receptor, Glucocorticoid receptor, Calcium-sensing receptor</td>
</tr>
<tr>
<td>Cytokines, growth factors, and receptors</td>
<td>IGF-I, IL-6, IL-1 β, IL-1RA, TNFR2, BMP-4</td>
</tr>
<tr>
<td>Bone matrix</td>
<td>COLIA1, Osteocalcin, Collagenase, α HS2 glycoprotein</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>ApoE, MTHFR, P57 Kip, HLA, PPAR γ, Werner Helicase gene</td>
</tr>
</tbody>
</table>

PTHR1, PTH receptor type 1; IL-1RA, IL-1 receptor antagonist; TNFR2, TNF receptor type 2; BMP-4, bone morphogenic protein 4; MTHFR, methylene tetrahydrofolate reductase; HLA, human leucocyte antigen.
ulation prevalence of COLIA1 Sp1 alleles; the polymorphism is common in Caucasian populations, but is rare in Africans and Asians (50). The mechanism by which the Sp1 polymorphism predisposes to osteoporosis has been investigated by Mann et al. (46) who found that the “s” allele had increased affinity for Sp1 protein binding and was associated with elevated allele-specific transcription in heterozygotes. These abnormalities were accompanied by increased production of the α1 chain of collagen by osteoblasts cultured from “Ss” heterozygotes, resulting in an increased ratio of the α1 to α2 chains and reflecting the presence of α1 homotrimer formation. Biomechanical testing of bone samples from “Ss” heterozygotes showed reduced bone strength compared with “SS” homozygotes and a slight reduction of mineralization of bone. Overall, the data suggest that the COLIA1 Sp1 polymorphism is a functional variant that has adverse effects on bone composition and mechanical strength.

Haplotype analysis has shown that susceptibility to fracture is probably driven by the Sp1 polymorphism rather than other polymorphisms within the COLIA1 gene (51), although recently two polymorphisms have been described in the promoter of COLIA1 that are in LD with the Sp1 polymorphism and are also associated with BMD (52). Further work will be required to assess the functional significance of these polymorphisms and determine whether they interact with the Sp1 polymorphism to regulate BMD and bone fragility. From a clinical viewpoint, the COLIA1 polymorphism may be of value as a marker of osteoporotic fracture risk, because it predicts fractures that are independent of BMD and interacts with BMD to enhance fracture prediction (53).

**ERα gene**

The ERα is a strong candidate gene for osteoporosis in view of the relationship between estrogen deficiency and bone loss. An association has been reported between a TA repeat polymorphism in the ERα promoter and bone mass in Japanese, U.S., and European populations (54). Other investigators have reported positive associations between haplotypes defined by PvuII and XbaI polymorphisms in the first intron of the ERα gene and bone mass (55) as well as age at menopause (56). The TA repeat polymorphism and intronic polymorphisms are in strong LD with one another, but the molecular mechanism by which they influence bone mass is as yet unclear.

**TGFβ**

TGFβ-1 is a strong candidate gene for regulation of bone mass in view of its potent effects on bone cell activity and the fact that mutations in the latency activating peptide region of the gene cause the sclerotic bone dysplasia Camurati Engelmann disease (21). Several polymorphisms have been described at the TGFβ-1 gene locus, and these have been variously associated with BMD, osteoporotic fracture, biochemical markers of bone turnover, and circulating TGFβ-1 levels (25, 26). A polymorphism within exon 1, causing a leucine to proline protein coding change in the signal peptide has been shown to be associated with BMD and circulating TGFβ levels (25), but this is in LD with polymorphisms in the promoter (57), and so it is unclear whether the association is driven by the regulatory polymorphism, the exonic polymorphism, or a combination of both. Another rare polymorphism has been described close to the splice site in exon 5 (26), although it is not yet known whether this influences splicing. In summary, there is good evidence to suggest that TGFβ-1 is a candidate gene for the regulation of bone mass, but the mechanisms by which polymorphisms of the gene influence TGFβ function are unclear.

**Other genes**

Polymorphisms of several other candidate genes have been associated with bone mass and/or osteoporotic fracture in clinical studies (reviewed in Ref. 17). Associations have been described between several polymorphisms at the IL-6 locus, BMD, and bone turnover. Most interest has focused on a functional polymorphism in the IL-6 promoter that has been associated with bone mass and bone turnover (59). Two studies have looked at the possible associations between apolipoprotein E (ApoE) alleles and osteoporosis. In Japanese women, the ApoE4 allele was found to be associated with low bone mass (60), and in another study of U.S. women, the same allele was associated with osteoporotic fractures independent of bone mass (61). The mechanism by which ApoE alleles influence susceptibility to osteoporosis is unclear, but it has been suggested that they may influence hydroxylation of osteocalcin indirectly by effects on vitamin K transport. Several other candidate gene polymorphisms have been studied in relation to BMD, and these are listed in Table 3. Constraints of space preclude full discussion of these candidate genes, which for the most part, have been investigated in isolated studies with a relatively limited sample size. Further work will be required to confirm their role as genetic regulators of bone mass.

**Implications for clinical practice**

Studies on the genetic basis of osteoporosis have important implications for clinical practice. The genes that regulate BMD and bone fragility are potentially important targets for the design of new drugs that can be used to treat bone disease. Some genes such as SOST and LRP-5, which are responsible for monogenic bone diseases, have already attracted the interest of pharmaceutical companies in this respect.

Genetic markers will also be used as diagnostic tools in the assessment of individuals at risk of developing osteoporotic fractures. We already know that the BMD T-score value of −2.5, which is widely used as a treatment threshold for osteoporosis, identifies only a small proportion of individuals in the community who actually suffer fractures. Genetic markers of bone fragility or bone loss could be used alongside bone density measurements to help target preventative therapies to those individuals who are at risk of fracture. The most promising marker identified so far in this respect is the COLIA1 Sp1 polymorphism, which seems to predict fractures independent of BMD (53), although it is likely that further markers of bone fragility will also be identified in the future. Another use of genetic profiling would be to distinguish treatment responders from nonresponders (49) and to identify patients who might be at risk of developing un-
wished side effects. This is an area that has been little studied in the bone field, but one that is well developed in areas such as oncology and has tremendous future potential in all spheres of medicine (62).

Acknowledgments

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